Social And Legal Issues Of Biotechnology: An Educational Perspective[1]

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ABSTRACT. Recent developments in molecular biology, immunology, tissue culture, and embryo manipulation have considerably enhanced man's ability to change living organisms. Potential benefits to mankind have led to multi-billion dollar per year investments involving over 200 new companies and many existing enterprises. Although various scientific problems involved in genetic engineering were insurmountable until recently, many of these problems have now been at least partially solved. Concerns have shifted somewhat toward issues involving: 1) the legality of patenting new life forms; 2) the question of the need for regulation; 3) safety; and 4) the public perception of science. The development of a high-tech industry around basic biological science has left some researchers with divided interests and has, at the same time, led to useful collaboration between industry and academe. Universities will soon face new tests of the basic premise of the 'universality' of knowledge gained from research as they attempt to patent and temporarily withhold publication of proprietary discoveries made with taxpayers' support.

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INTRODUCTION

Biotechnology was recently defined as "any technique that uses living organisms (or parts of living organisms) to make or modify products, or to improve plants or animals, for beneficial use" (J. Wyngaarden; see National Institutes of Health 1985). This broad definition covers recombinant DNA techniques, monoclonal antibodies, gene engineering of higher organisms, and so on. It can also be loosely construed to include such traditional processes as the production of antibiotics and food processing by fermentation.

The fledgling biotechnology industry involves over 200 new companies and many established firms with annual capital investments of billions of dollars (Blumenthal et al. 1986). By contrast, sales of recombinant products for 1985 were estimated at $337 million (Emyanitoff and Weinert 1984). Thus, investment presently exceeds income from sales, and investors hope to profit by obtaining favorable patent and market positions.

The increasing ability of biologists to directly and specifically manipulate genes in living organisms is bringing about a revolution in the biological sciences. In some respects, the biotechnological methods bring about changes that are less dramatic than those produced by traditional breeding and mutagenesis, since they may involve one or a few specific gene functions instead of selection for gross phenotypic changes involving many genes. Nevertheless, the ability to produce specific changes in somatic and germ tissues of living organisms through genetic engineering has raised social and legal questions that remain unresolved. Perhaps the most compelling of these is the question of who controls living matter and its derivatives. This issue involves not only inventors' rights, but also the origin of the starting material and its progeny, the legal regulation of living "products" by the government, patentability of life forms, legal liability, and environmental factors. For educators, other issues are involved. Among them are assessment of future manpower needs, training programs, potential conflicts of interest, patent policy, secrecy, animal rights, and consortium agreements involving both the public and private sectors.

ECONOMICS OF BIOTECHNOLOGY DEVELOPMENT

Much of the enabling knowledge of the present revolution in molecular biology has come about in the United States as a result of federally sponsored research, particularly research sponsored by the National Institutes of Health (NIH). Projected expenditures for biotechnology research during the coming year are shown in Figure 1. By far the greatest source of government support is NIH. It is appropriate that the principal beneficiary of this research to date has been human medicine. In AIDS (Acquired Immune Deficiency Syndrome) research alone, the discovery of the agent, the determination of its total structure, elucidation of the mode of transmission, diag-

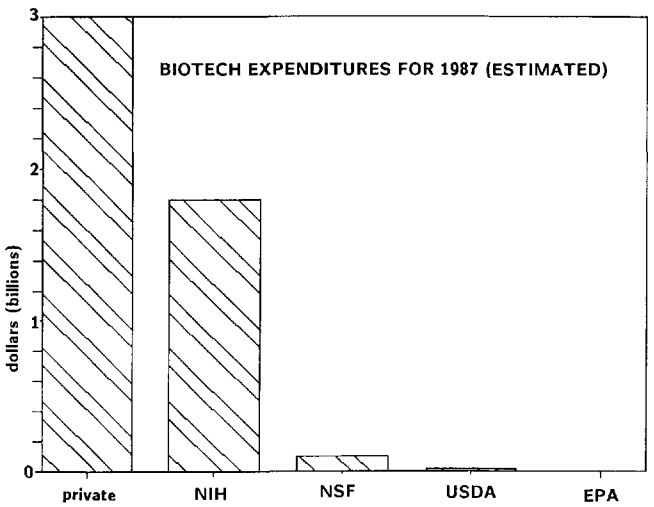

FIGURE 1. Estimated sources of funds for biotechnology research and development in 1987. Data compiled from Blumenthal et al. (1986), Wyngaarden (1985), and Shoemaker (1986). NIH, National Institute of Health; NSF, National Science Foundation; EPA, Environmental Protection Agency; USDA, U.S. Department of Agriculture.

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nosis of infection, and present vaccine development efforts have all hinged on the use of the new molecular genetics. Other examples of the benefits of molecular biology in human medicine are too numerous to mention. Altogether, federal commitments to biotechnology development total about $2 billion. This large contribution has given the United States the leading edge in biotechnology development. In the private sector, new corporations as well as established companies and limited venture partnerships have also invested heavily. To date, several billion dollars have been allocated to biotechnology development, making these contributions a prominant factor in the overall development of a new industry. In addition, a recent study from the Center for Health Policy and Management, Harvard University (Blumenthal et al. 1986) suggested that the private industries are spending an additional $136 million annually to support biotechnology research in universities.

Despite the benefits, biotechnology (and other health related) funding is small compared to other federal expenditures. For example, the entire annual budget (approx. $5 billion) for all of NIH in 1986 was less than 2% of the amount spent each year for defense. The proposed space platform alone would cost more than three years of budgeting for NIH. A comparison of NIH with other federal research spending, reflecting relative national priorities, is shown in Figure 2.

Sale of biotechnology products (e.g., recombinant hormones, pharmaceuticals) is just beginning. Estimates suggest that sales will increase exponentially for a number of years in that market (Emyanitoff and Weinert 1984). The need for materials such as recombinant bovine growth hormone, which is used to increase milk production in cows, will undoubtedly create lucrative and unforeseen markets for novel pharmaceutical products. For example, Genentech Corporation plans to sell $700 million per year of its recombinant plasminogen activator (Nakaso 1987) by 1990. In agriculture, applications of genetic manipulation are potentially great, but no comprehensive assessment of the overall impact can yet be made, particularly since neither recombinant animals nor plants have been marketed.

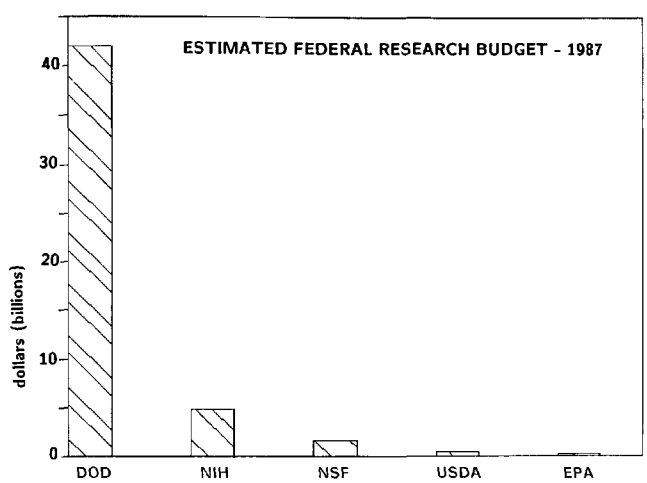

FIGURE 2. Disposition of estimated federal research budget for 1987. Data compiled from Smith (1986) and Shoemaker (1986). DOD, Department of Defense. For names of other agencies, see Figure 1.

The potential exists for genetic improvement in all agricultural crops and animals. Attempts are being made to use genetic engineering to develop resistance to pests and pesticides, to change the nutritional value of food proteins, to increase the size of meat animals, and to insert nitrogen fixation genes into plants. It is likely that all of our common food species will be altered eventually by direct genetic manipulation. In addition, recombinant animal vaccines are being developed that promise to provide resistance to diseases such as swine pseudo-rabies. Specific examples and up-to-date information on industrial research and development are reported monthly in *Genetic Engineering News* (published by Mary Ann Leibert, Inc., 1651 Third Ave., New York, NY 10128). Finally, it is even likely that "molecular farming" will enable produce animals such as cows and chickens to secrete recombinant proteins in their milk and eggs. Thus, a sector of the agricultural economy, which is currently depressed and burdened with surplus, could be used effectively to produce polymers, enzymes, nutritional proteins, antibodies, vaccines, and hormones. Steady improvements in the methods of recombinant protein production should enable many industrial products to be made on an agricultural scale by the year 2000. Ohio enterprises that have already contributed substantial resources to biotechnology development include Sohio (Cleveland), Monsanto (Columbus), Battelle Memorial Institute (Columbus), Stolle Research and Development Corporation (Cincinnati), Technology Unlimited (Wooster), Enzyme Technology Corporation (Ashland), Life Technologies (Chagrin Falls), and Embyrogen (Athens).

MANPOWER NEEDS

A recent issue of *Science* (18 July 1986) contained 118 job advertisements in all disciplines ranging from administrators to laboratory technicians. Sixty-one (>51%) of these involved some aspect of biotechnology or molecular genetics. Data from the Bureau of Labor Statistics indicate that by 1990 about 37,000 individuals trained in areas underlying biotechnology will be needed (R. Christophersson; see NIH 1985). One problem is that training can take as long as 10 to 14 years (college, doctoral, and post-doctoral training) for a Ph.D. Substantial lead time is therefore needed to train new people. Industry can be expected to attract many of the more promising individuals by offering higher salaries than most universities can afford to pay. Thus, fewer scientists with doctorates will remain in academe to train new biotechnologists, creating a further shortage of trained people. Obviously, a strong science and mathematics background in high school will be essential if these candidates are to succeed. It should be recognized that many of our present scientists were trained before the deemphasis of science and mathematics education and the subsequent lowering of achievement test scores that became apparent during the 1960s and 1970s. Thus, it may be especially difficult to train students in the present era. The education of a good scientist must begin in the primary school.

The types of personnel needed in the biotechnology industry are apt to be quite varied. Typically, a laboratory consists of a principal investigator (Ph.D. or equivalent), research associates, post-doctoral fellows, students, tech-

nicians, and support personnel. In addition, there will be work for patent attorneys and people with MBAs who are knowledgeable in the biological sciences. Table I lists some of the types of jobs presently available in university and industrial laboratories, and a typical range of salaries.

Of those awarded the doctorate in biological science in 1983, 67% were male; 86% were American; average age at graduation was 30; and matriculation time from B.A./B.S. to Ph.D. averaged 6.2 years. One-half held Master's degrees as well as the doctorate; 67% went on to post-doctoral studies. One-half worked in research and development; 30% did some teaching (National Research Council 1983). For a student interested in biotechnology-related jobs, recommended courses of study would include basic science (i.e., chemistry, physics, biological sciences) in high school and college, mathematics through calculus, and appropriate graduate training in the area of interest.

Training in biotechnology specialties is available through several types of programs. For example, a number of short course topics are offered at Catholic University in Washington, DC, Michigan State University in East Lansing, and at Cold Spring Harbor Laboratories in New York. In Ohio, graduate level molecular biology workshops are offered in the summer at The Ohio State University's Agricultural Research and Development Center in Wooster. Graduate programs in cell and molecular biology are available at The Ohio State University in Columbus, at Ohio University in Athens, at Miami University in Oxford, at the University of Cincinnati, and at Case Western Reserve University in Cleveland. A biotechnology program leading to a B.S. degree is offered by the Rochester Institute of Technology in Rochester, NY. Massachusetts Institute of Technology has been awarded substantial funding from the National Science Foundation to establish a biotechnology center, including biotechnology training, and the University of Minnesota has an interdisciplinary Master's level program in bioengineering. At this early time in the growth of the industry, it would be difficult to speculate on the number, type, or quality of jobs that will be available in future years. Technology development, government regulatory practices, and foreign competition will play a major role in shaping the result.

TABLE 1

Salaries of biotechnology workers

Job title	Training required	Approximate salary (1986 dollars)
Principal Investigator	Ph.D (or equivalent) plus 2-5 years post-doctoral training.	30,000-100,000
Post-Doctoral Fellow	Ph.D. (or equivalent) in appropriate biotechnology discipline	13,000- 40,000
Research Associate	Ph.D., or M.S. and equivalent experience.	13,000- 40,000
Pre-Doctoral Fellow (Research Assistant, Teaching Assistant)	Bachelor's degree or M.S. in appropriate scientific discipline; candidacy in graduate program.	5,000- 15,000
Technician	High School or Associate degree	9,000- 18,000
Technician	Bachelor's degree	12,000- 30,000
Technician	Master's degree	15,000- 45,000

FUTURE REGULATION OF BIOTECHNOLOGY

Until recently, most research in molecular genetics was regulated by the Recombinant DNA Guidelines established by NIH in the wake of the Asilomar Conference on recombinant DNA safety in 1975. Over the years, many of the safety concerns about recombinant DNA research have been dealt with through careful study and the development of simple biological containment features in conjunction with "common sense" physical containment. The original NIH Guidelines for Recombinant DNA Research have been simplified greatly, and many recombinant experiments can now be conducted exempt from regulation.

The essence of the present highly successful system is a form of 'negative regulation.' First, the recombinant guidelines are a voluntary set of restrictions that are mandatory for federal grantee institutions, but that are almost universally accepted by industry, academe, and a number of foreign countries. Second, the guidelines do not attempt to approve specific projects that fall under broad, general headings; instead, they simply specify the containment level necessary, if any. Potentially hazardous experiments are kept at a higher level of biosafety, and are subject to review by institutional biosafety committees, by the Recombinant Advisory Committee (RAC), or by the Director of NIH. Negative regulation frees RAC of the necessity to approve most experiments.

More recently, experiments with viral gene vectors, recombinant animals and plants, planned experiments in human gene therapy, and others have raised questions that the guidelines do not specifically address. Many government regulatory agencies have subsequently claimed jurisdiction. These include the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), the White House Office of Science and Technology Policy (OSTP), and NIH-RAC (OSTP 1986). It remains to be seen if such a multi-agency consortium can function effectively.

A major problem in regulation is the definition of biotechnology itself and the conflicting regulatory paradigm that biotechnology should be regulated no differently than anything else. For example, in the new proposed Federal Regulatory Guidelines from the Office of Science and Technology Policy (1986), the FDA (p. 23309) stated that regulation "must be based on the rational and scientific evaluation of a product, and not on *a priori* assumptions about certain processes." Later, the FDA (p. 23309) reversed the argument stating that "new marketing applications will be required for most products manufactured using new biotechnology," even if they are identical to other products. Thus, there is conflict within the regulatory agencies concerning whether products or processes are being regulated. Yet another concern in the new regulatory guidelines is the concept of regulating only "new" biotechnology. Apparently, the old products (i.e., those associated with present jobs and markets) are politically taboo. An example of this is found in the proposed definition of pathogenic organisms. This definition includes all common animal gene expression vectors (which are based on low-risk viruses), as well as

guidelines-exempt, bacterial gene-cloning systems involving gene vectors such as the bacterial viruses pBR-322 and bacteriophage lambda. The exception is then made (p. 23333) for those pathogens "used for laboratory research or commercial purposes and generally recognized as nonpathogenic." This appears to "grandfather" the current vectors, while inhibiting the development or use of the new generation of vectors that are potentially better than those developed with previous technology.

There are probably several areas of legitimate regulatory concern. These include potential alteration of the environment made by recombinant organisms, infectivity of certain gene vector systems, and the production of toxic, dangerous, or addicting substances by altered organisms. It remains to be seen how the courts will handle liability and perceived risk issues.

A possible impediment to biotechnology development in the United States is the current litigious climate. The concepts of a risk-free society and cradle-to-grave security have created "glitches" in the legal system that allow a single individual to halt important scientific projects. For example, Rifkin (1983) has successfully used the courts to stop genetic engineering projects by invoking the need for environmental impact statements. Recently, a highly promising vaccine against swine pseudo-rabies was recalled because it involved a deletion of genetic material from the virus. It is interesting that less precise genetic alterations and deletions made with the old technology are acceptable for vaccine development, even though they are not well understood. It is clear that lawyers, judges, and the public will react out of fear and ignorance if they do not understand the processes involved. Daniel Koshland, Jr., Editor of *Science,* recently commented (1985): "What concerns me is that some of the fundamental concepts and methodologies of science are outside the understanding of the vast majority of the population, including its opinion makers . . . political and civic decisions are frequently made . . . with no attempt to obtain a control sample." In one instance, Congressional leaders attempted to force the U.S. Patent Office to grant a patent on a 'perpetual motion machine', although the machine had failed tests performed by the Patent Office. Dr. Koshland also observed that: "We watch with consternation as society acts as if zero risk could be achieved." It is true that the eternal safety of any living organism cannot be guaranteed since the organism is subject to reproduction, further change, growth, and adaptation. Therefore, some risk assessment and the acceptance of minimal risks will be required if newly altered organisms are to be developed. Some feel that Rifkin's challenge will help to bring a thorough review of the whole process of biotechnology regulation and safety.

Finally, there is growing public concern for the treatment and regulation of animals in research. Although it seems axiomatic that researchers would humanely treat the animals used in biomedical research, there have been several highly publicized examples where laboratories have been broken into, disagreeable pictures suggesting animal mistreatment were taken, and in some cases, animals were 'liberated' (Fox 1984). Laws and regulations are changing to reflect the public perception of scientists and their work. However, tighter regulation and increased paper work on laboratory animals add greatly to the cost to the public of animal research. Another problem for researchers is that required reports made to the institutional laboratory animal care and use committees are disclosed as public information, which may jeopardize or invalidate future university and corporate patent applications. This, in turn, may negate the flow of dollars from industry into mutually profitable research in universities. Recently, bills have been proposed in Ohio and elsewhere that would prohibit the use of pound animals in research. This would require the substitution of animals bred specifically at greatly increased cost (Fox 1984). Since many pound animals would normally be killed, it is not clear how the plan would benefit animals.

Concerned scientist groups such as the Scientist's Center for Animal Welfare in the Washington, DC area are beginning to take a more active role in regulating their own use of animals. There is a movement afoot to eliminate painful and unnecessary tests (e.g., the Draize test, where toxic substances are placed in rabbits' eyes), and to substitute the use of cell culture or test-tube types of analyses for animal work wherever possible. Such reform is long overdue.

The use of the animal model will probably continue to be an important proving ground for biomedical and biotechnological research. The American Society for Microbiology (ASM) in a recent position statement (Wodzinsky 1986) has said, "ASM believes that the use of animals in research is necessary if progress is going to be made in improving the quality of life and longevity of humans and animals."

TECHNOLOGY DEVELOPMENT: INTERACTION BETWEEN PRIVATE AND PUBLIC SECTORS

A traditional academic paradigm (anecdotal) states that industry profits from technology by focusing on development, marketing, patent protection, and trade secrets, whereas universities do mostly basic research and report the results publicly. The result has been a lack of knowledge in the area known as 'generic applied research', linking basic science to applied research. These bridging technologies have been considered a focus of cooperation between industry and academe (N. Newell; see NIH 1985).

Based on a recent study (Blumenthal et al. 1986), it is estimated that there may be over 350 companies in the United States practicing some form of biotechnology. These firms contribute about $120 million to biotechnology research projects and universities. On the average, this type of research yields the company four times as many patents per dollar as corporate, in-house research. Altogether, these companies spend close to $3 billion per year on biotechnology development (Fig. 1). The amount spent on university research by the private sector represents 16% of the total biotechnology research budget in the universities. It relieves some companies of the need to acquire certain unobtainable assets such as access to a biomedical library or specialized laboratory resources that may not be needed permanently.

There are also caveats and dangers in these associations that must be surmounted. It is often heard that universities must protect freedom of information and the 'universality' of knowledge. Corporate patent policy can

infringe upon this responsibility. Recently, Varrin and Kukich (1985) formulated a useful set of guidelines that can be used to develop consortia agreements between academe and industry. These are designed to protect the interests of both parties without compromising patentability, graduate students' rights, or the obligation of universities to publish their results. An example of a viable consortial agreement (Olson 1986) is the contract between the Monsanto Company and Washington University School of Medicine. Such contracts preserve investigator initiative, student participation, and timely publication of results.

OTHER ETHICAL ISSUES

Many of the ethical issues facing the new industry have already been addressed to some extent through the last 13 years of experience with recombinant DNA. Issues that have recently emerged include questions of human gene engineering and permanent alteration of the germ line.

Presently, human gene engineering is in the planning stages. Serious proposals for somatic cell gene therapy are being considered for comment at NIH. These involve treatment of the cells of an individual in order to insert a key gene that is defective or missing in the afflicted individual. A major candidate for gene therapy is the gene defect responsible for Lesch-Nyhan syndrome. The critical factor in somatic cell gene therapy is that only certain cells of the individual are being treated. The method of choice is to insert the "repaired" gene into a defective virus that delivers it stably into the chromosomes of the target cells of the afflicted individual. The technique works in mice (Williams et al. 1984); several groups plan to try it in humans during the next few years. There is relatively little controversy regarding the science since it does not involve permanent alteration of the individual's germ cells (i.e., it cannot be passed on to offspring). The major technical achievement is to devise adequate "suicide" vectors or gene delivery systems that will have sufficient biological containment built in to insure safety and prevent reinfection.

The larger issue of permanent alteration of the human germ line remains unsolved. The techniques for germ line alteration already exist and have been used successfully in a number of animal species. There is no doubt that agriculture will be permanently affected by this technology. Virtually all scientists agree, however, that it is still too early to attempt the germ line experiments on humans. If and when such experiments are approved, it will be after much public comment and debate and after ample consideration by NIH and by RAC.

In nature, alterations of the germ line are rather frequent. In most species examined, including *Homo sapiens*, there are many examples of the existence of viral insertions (retrotransposons) caused by agents similar to those used by molecular biologists as gene insertion tools (for a review, see Rogers 1984 or Baltimore 1985). Events associated with viral insertion probably resulted in the 300,000 or so *Alu* repeats found in human chromosomes. Thus, viral infections are a major natural shaping force of the genome. Some of the viruses are xenotropic; that is, they are able to transport genes from one species to another. Since the genetic code is universal, the transported genes may be well-adapted to the new host when they move in. Living organisms are the products of natural genetic mobility. Gene sequences reveal many examples of natural editing and splicing. This ability to efficiently move genetic material in nature may provide important clues toward understanding rapid evolutionary shifts that have occurred at certain times (Erwin and Valentine 1984). Nevertheless, the use of such natural gene vectors to permanently alter the human germ line must await considerable animal experimentation and scrutiny. The mere availability of the technology does not herald the advisability of such experiments.

NEW TECHNOLOGY PATENTS

In 1980, a U.S. Supreme Court decision, Diamond vs. Chakrabarty, made possible the patenting of genetically engineered microorganisms. That same year, the Cohen-Boyer patent on the process for the construction of recombinant DNA molecules was issued (for a review, see Olson 1986). Patents provide 17 years of protection for inventions that meet three criteria: they must be unobvious, original, and useful. As the technology has advanced, many patent issues have emerged. Does the Chakrabarty decision apply to patents on higher organisms as well? Which parties hold rights when living cell lines or organisms are patented? For instance, does the donor of a useful cell line retain a proprietary interest? Who is liable for living organisms or their progeny?

The patenting of new technology is also an issue that involves our universities. Some university patents have been extremely profitable and university patent policies are presently leaning toward sharing royalty with faculty inventors. This incentive may allow the recruitment of excellent staff that the universities could not otherwise afford, as well as provide incentive to generate profitable new technology. In order to obtain an international patent, the inventors must not have publicly disclosed proprietary knowledge of the invention prior to the patent application. Hence, there can be a delay of several months between an invention and the time that it can be published. This delay is normally not a problem unless it prevents a student from graduating on time. Efforts should be made not to involve students in proprietary research if involvement will slow their progress. There is also the question of whether universities should use taxpayer dollars to develop patents that will involve restricted use of inventions. This issue becomes increasingly difficult as more and more faculty start new corporations that may benefit from the technology. There is a general opinion that the use of university facilities for personal corporate activities constitutes a conflict of interest (Varrin and Kukich 1985). Faculty members should disclose their corporate interests and keep them clearly separate from their academic jobs. To do otherwise would allow faculty interests to be compromised.

The issue of what life forms are patentable remains largely unresolved. Again, the biotechnological education of lawyers, judges, and patent officials will be tested as we enter this new legal arena.

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